THE PHYSIOLOGY OF FERTILITY IN MAN AND MONKEY*

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HUMAN fertility has always been a subject of far greater moment to politicians and vital statisticians than to biologists. A reproductive machine that on almost all sides was presumed to work too well, whose infinite capacities for multiplication could raise the spectre of the complete exhaustion of the world's supply of food, appeared too obvious in its manner of working to attract the strong interest of scientists; neither did it require their close attention in order to discover means for preventing its free expression. Malthusian doctrine presented to the world the menace of unbounded human fertility. Sterility, as Enid Charles has written, became enthroned as one of the cardinal virtues.† It is thus no matter for surprise that the physiological problems of man's own fertility, unlike that of his domestic animals, were something to be ignored rather than investigated. The last few years have seen the beginnings of a complete change in point of view. Kuczynski's new methods of population analy is have emphasized the fact that reproduction, both in North-West Europe and in other regions inhabited by Europeans, is proceeding at so dangerously slow a rate that, unless a pronounced change in its trend occurs, the populations concerned will soon be greatly diminished in numbers, and profoundly altered in age-group constitutions.‡ A similar trend has been diagnosed in countries as recently industrialised as Japan, and I am guilty of little or no exaggeration in saying that, in general, human reproduction and replacement are to-day taking place at as slow a rate as is compatible with survival, and that in certain regions of the globe even this is not being achieved. The human reproductive machine no longer appears a dangerously perfect mechanism.

It is not my function in this lecture to examine the modern trend in population growth, nor to discuss the sociological factors, economic and psychological, that have brought it about. Neither is it my business to discuss the biological problems concerned with the deliberate limitation of fertility. My task is to consider the physiological events which are concerned in the full expression of human fecundity. The basic facts, which will be treated more closely later, can be simply stated. A normal adult woman has about thirty years of reproductive life. At most thirteen, and frequently fewer, times a year she liberates at twenty-eight-day intervals what is almost always a single ovum. Each ovum lives at most a day. Unless insemination occurs frequently, the chances of an ovum meeting a viable sperm are remarkably few (for sperms have a correspondingly short life). When pregnancy, and then lactation, supervene, further ovulation and further conception are inhibited for some twelve months.

Thus assuming a woman to be reproducing at a theoretical maximum rate, and disregarding the possibility of multiple births, she could produce some thirty offspring in her lifetime. Whether or not any woman has achieved such fruitfulness I do not know. When viewed against the picture of fertility in the rest of the animal world, such theoretically maximal fecundity would, however,

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† Charles, E. 1934. *The Twilight of Parenthood.* London. Watts.

‡ Charles, E. *Ibid.*
—— 1935. *Roy. Econ. Soc.*, Mem. 55.
Kuczynski, R. R. 1935. *Economica, 2,* (N.S.), 128.

not be excessive. The replacement rates of certain fish, even allowing for the incredible mortality which prevents more than ten or fewer in a million surviving to maturity, are enormously higher. Indeed, as low a limit of fertility as that of Man finds its counterpart perhaps only among a few other mammals.

Even if a theoretical maximum output is regarded as its measure of efficiency, the human reproduction machine is thus clearly inferior to that of almost all other living things. The theoretical maximum output in Man is however ridiculously in excess of the actual reproduction rate. I am not, as I have said, going to deal with the deliberate measures, which, following on a fairly widespread acceptance of the relation between insemination and conception, are taken by Man in order to prevent reproduction. There are, however, many limiting factors to reproduction which operate without any general awareness of their existence, and which to a large extent are uncontrollable. For example there are those limitations to more frequent sexual behaviour, and to a richer reproductive life which, as Hogben has argued,* are an automatic outcome of modern developments in social hygiene, and in the technique of living generally. With these limitations, also, we need not concern ourselves in this lecture. On the other hand, physiological and pathological processes which militate against a richer fertility need to be briefly considered before we examine the phenomena of ovulation and fertilization, the two events which in the last analysis, impose the conditions whose satisfaction is essential to fertility. The wider limiting factors can be divided into two groups: first, the general physiological factors (for example those which demarcate the total period of a woman's reproductive life) that affect all women: second, those special genetical and pathological factors which contribute to the production of differential fertility.

* Hogben, L. 1931. *Genetic Principles in Medicine and Social Science.* London. Williams and Norgate.

GENERAL PHYSIOLOGICAL LIMITING FACTORS

Seasonal Variations in Birth-Rate

Most vertebrates are incapable of reproduction except during one period of the year, different species having different breeding seasons. Thus polar bears are born only during the middle of winter, while all Californian sea-lions see the world for the first time between June 15th and July 15th. If a female polar bear fails to conceive, or does not mate, during the mating season which precedes the general "birthday" of its species, it cannot again become pregnant until the succeeding mating period. This is an obvious restriction to fertility, from which, however, Man does not suffer. For him birthdays are an event for the individual, not for the species. All the members of our zoological order, the Primates, are not the same in this respect.* Thus most lemurs have a restricted breeding season, and the same may possibly be true of a few of the South American monkeys. On the other hand the available evidence for Old World monkeys and apes clearly suggests that these animals breed at all times. It also shows that marked seasonal variation may occur in their birth-rates. For example, most Hamadryas baboons are born in November, while April to June are the favoured months for births among Rhesus monkeys. This fact either implies that some months of the year are unfavourable for ovulation and spermatogenesis, or that the particular physiological processes which act as a spur to overt sexual behaviour slow down at those times. Two such mechanisms inhibiting reproduction could operate together. Whatever is the correct explanation, there can be no doubt, since monkeys always have the opportunity for mating, that seasonal variations in their birth-rates are physiologically determined.

Seasonal variations also occur in the human birth-rates of certain countries.† They show themselves better, I understand,

* See Zuckerman, S. 1932. *Proc. Zool. Soc.*, London, p. 1059.

† See Marshall, F. H. A. 1922. *The Physiology of Reproduction.* London. Longmans, Green and Co.

in data relating to illegitimate than in data regarding legitimate births. While most observers ascribe all the variations that occur to social traditions and economic causes, some infer from such facts as the greater frequency of conceptions in parts of the Northern hemisphere during spring and mid-summer, an innate tendency to greater reproductive capacity at those times. The love feasts and related festivals of certain peoples are also regarded as evidence pointing to the same conclusion. Such data are obviously very unsatisfactory for drawing conclusions. At present, the strongest support for the view that Man's reproductive capacities may vary seasonally owing to *uncontrollable physiological* factors would seem to come from the fact that the reproductive capacities of monkeys do. This, however, is poor support. The question is a significant one, and if there are undiscovered physiological factors which tend to reduce human fertility at certain times of the year, they should be sought for.

Puberty and Menopause

The most obvious limitations to human fertility are set by puberty and the menopause, and my chief excuse for discussing these topics to-day, is first, the not-remote possibility that both will become controllable events, and second, the growing recognition that puberty and reproductive capacity are not synonymous terms.

The physiological activity of the gonads is dependent on the functioning of the anterior lobe of the pituitary. If this organ is removed from an experimental animal, the ovaries or testes, and the accessory reproductive organs (which in turn are dependent on the testicular or ovarian secretions), all atrophy. If some other animal's pituitary is implanted into one whose pituitary gland has been removed, the reproductive organs again become functional. If the same experiment is done with immature animals—in particular females—the reproductive organs immediately mature and become active. Moreover they can be maintained in that condition by adequate administration of the activating substances of the pituitary.

Puberty and the menopause are generally believed to be controlled by the anterior lobe of the pituitary. During infancy and childhood, the gland does not elaborate its gonadotropic secretions, for the reason, according to some, that it is then actively promoting growth. As the process of active growth slows up, the gland begins to pour its reproductive hormones into the circulation, and these immediately affect the ovaries or testes, as the case may be, both by promoting the secretion of their essential hormones (which in turn act on the accessory reproductive organs), and by stimulating the maturation of sperms or ova. The number of separate gonadotropic hormones produced by the pituitary is still disputed. Some workers hold that a single factor is responsible not only for the growth of the ovarian follicles but also for their rupture (ovulation), and for the conversion of the ruptured follicles into corpora lutea, organs of internal secretion whose hormonal products are concerned in maternal processes. Other investigators believe that more than one gonadotropic factor exists.

Only the first phase of the full ovulation cycle is experienced for a long period after the process of reproductive maturation (puberty) sets in both in Man and monkeys. The anterior lobe of the pituitary presumably undergoes waves of activity during which it elaborates only a follicular-maturation hormone, or only enough of a general gonadotropic hormone, to cause development of the ovarian follicles. The hormone produced by the developing follicles causes growth of the uterine mucosa, and when the wave of pituitary activity comes to an end, the wave of follicular growth it stimulated also ceases, so that the uterus no longer comes under the influence of the follicular hormone. As a result, a retrogressive uterine phase sets in and menstruation occurs. The first menstrual cycles after puberty probably always follow this course, *i.e.*, the first menstrual cycles experienced by women are usually unaccompanied by ovulation.* Hence it

* See Hartman, C. G. 1931. *Science*, *74*, 226.
Mikulicz-Radecki, F. v., and Kausch, E. 1935. *Zentralbl. f. Gyn.*, p. 2290.

was that the Trobriand Islanders studied by Malinowski never conceived in their early youth in spite of unrestricted sexual licence.* Hence, too, births rarely occur before the third year of effective marital relationship in Indian "child marriages."

Monkeys and apes show a similar latent period between the onset of puberty and the attainment of effective reproductivity. It seems likely that this latent period is a physiological characteristic that applies generally to all Old World Primates—allowing of course for the usual individual exceptions. If the present growth of knowledge of pituitary mechanisms is maintained, there can be little doubt that before long the process of puberty will be amenable—if such a thing is ever required—to deliberate control.

As maturation proceeds, the waves of pituitary gonadotropic activity become more effective, and determine complete cycles of follicular growth, including both ovulation and corpus luteum formation. Conception then becomes possible, and continues possible in almost every cycle until the menopause. I use the word "almost" deliberately, for it has been thoroughly established on monkeys,† and the fact confirmed clinically on women,‡ that ovulation may fail to occur during some menstrual cycles of completely healthy individuals. The clinical evidence is derived from chance observations made during abdominal operations, and from observations of curettings of the uterine lining, which takes on characteristic and unmistakable appearances in respect to the occurrence or non-occurrence of ovulation. The failure of ovulation is no doubt often due to some aberration of pituitary function, the cause of which is at present unknown. Though it is said that some women can tell, by the appreciation of mammary gland changes, whether or not they have ovulated in any given cycle, there is no means of prophesying about the possible occurrence or non-occurrence of future ovulations. It is, of course, conceivable that some women are more prone to anovulatory cycles than are others, and that they are consequently less fertile.

The occurrence of anovulatory cycles raises the interesting question of their possible relation to the well-known fact, which has been established statistically, that fertility decreases progressively from almost the beginning of the child-bearing period. Figures which display this fact well are those relating to births in Sweden in 1891, data which, according to Charles,* are widely used as a standard of comparison by authorities on population in this country.

Birth-rates per 1,000 *wives in different age groups*

15-19	...	518
20-24	...	451
25-29	...	375
30-34	...	312
35-39	...	250
40-44	...	142
45-49	...	20

It has been suggested, so I understand, that these data indicate that the reproductive capacity of normal healthy women, as a result of specific and uncontrollable physiological factors, decreases almost from the moment of its establishment. The fact, pointed out by Charles, that "the fertility of newly married women of a given age is greater than that of women of the same age who have been married longer" would, however, seem to argue against this view, except, of course, that it would still be possible to maintain that such a decline always begins only after the start of actual reproduction. If physiological factors are responsible for the progressive decrease in fertility, they must operate either by decreasing the incidence of ovulation, or by increasing the incidence of abortion. It is also possible that spermatotoxins are produced in the body of the female, which act

* Malinowski, B. 1932. *The Sexual Life of Savages.* London. Routledge.

† Corner, G. W. 1927. *J. Amer. Med. Assoc., 89,* 1838.

‡ Allen, E., Pratt, J. P., Newell, Q. U., and Bland, L. J. 1930. *Contrib. Embryol.*, Carnegie Inst. Washington, *22*, 45.
Novak, E. 1930. *J. Amer. Med. Assoc., 94,* 833.

* Charles, E. 1934. *The Twilight of Parenthood.* London. Watts.

adversely on sperms.* It is, however, even more likely that both the practice of contraception and a decreased incidence of coitus are also involved in the progressive decrease in the relative frequency of births during the child-bearing period. The problem raises an important issue in the consideration of fertility, and the difficulty of separating deliberately contrived influences from those that are physiologically determined (both of which may be operating in producing the effect of a diminishing fertility in Man), makes it essential that the question be examined on laboratory animals. Investigation of monkeys or apes would provide the most useful information, since they are most akin to us zoologically, but to my knowledge they have not been studied from this point of view. In some other animals that have been investigated, for example mice†, there does appear to be an inverse relation between the degree of parity and the number of young born per litter.

All ovarian activity comes to an end after the menopause sets in, usually between the ages of 45 and 50. The menopause is probably a more gradual and less abrupt event than it is popularly supposed to be. During its establishment ovulation first becomes irregular before ceasing altogether. It is to chance and unexpected ovulations occurring after the menopause is supposed to have taken place that many late pregnancies are due.

It is not altogether certain that the post-menopausal cessation of ovarian activity is due to a decline in the gonadotropic activity of the pituitary. The urine of post-menopausal and castrated women contains large quantities of that fraction of the gonadotropic hormone which promotes growth of the ovarian follicles.‡ It is conceivable that the initial menopausal change lies in the ovaries themselves, and is such as to raise their threshold to the gonadotropic hormones of the pituitary. In view of the desirability of exercising some control over the menopause, not only from the clinical but also from the point of view of prolonging reproductive life, it is obviously necessary that the phenonemon should be more closely studied in laboratory animals than it has been.

The human male, as is well known, does not suffer so abrupt a menopause as do women. Some writers describe a corresponding but slower process in men, occurring as a rule at some time during the sixties. Exceptions are nevertheless very frequent. Motile and possibly fertile sperms have been recovered from a man of 95.*

So far I have considered only general physiological factors that limit fertility. Before passing on to what can be termed differential limiting factors, there is one further normal physiological limiting factor that I shall just mention—namely the number of ova a woman liberates at a single ovulation. Usually, of course, it is one, and twins are born only once in about eighty-seven births. The single ovulation of Man is a characteristic inherited from, or perhaps better expressed as belonging to, the whole group of Old World Primates from which Man springs. Twin births among African and Asiatic monkeys and apes appear to be at least as rare as they are in Man.†

DIFFERENTIAL LIMITING FACTORS

It has been estimated that 10 per cent. of marriages in which no contraceptive measures are taken prove sterile.‡ Such sterility depends on a variety of factors, whose consideration properly belongs to clinical discussions of sterility rather than to a lecture such as this. A brief outline of the factors concerned would not, however, be out of place.

Genetical Factors

I would first remind you of the widely accepted belief that some otherwise normal

* See Pommerenke, W. T. 1928. *Physiol. Zool.*, *1*, 97.

† Parkes, A. S. 1924. *Brit. J. Exper. Biol.*, *2*, 21. See also Marshall, F. H. A. *Loc. cit.* p. 38.

‡ See Frank, R. T. 1935. in *Glandular Physiology and Therapy*. Chicago. Amer. Med. Assoc.

* See Forsdike, S. F. 1928. *Sterility in Women*. London. Lewis.

† See Yerkes, R. M. 1934. *Science*, *79*, 430.

‡ Meaker, S. R. 1934. *Human Sterility*. London. Baillière, Tindall, & Cox.

people may be poor breeders, and that a low fertility may thus have a genetic basis. Numerous corresponding instances of low and high fertility are known in animal husbandry. The Leghorn fowl, for example, lays many more eggs per year than do other breeds of fowl. The Dorset Horn sheep is outstandingly prolific. Hammond, again, has isolated two definite strains of rabbits, differing genetically, with widely different fertility rates.* The immediate factors affecting biological differential fertility are varied, but may roughly be grouped as (*a*) those which influence the number of ovulations, (*b*) those which affect the number of sperms liberated, and (*c*) those which determine the extent to which fœtal atrophy occurs.

It has at times been suggested that basic genetic factors lie behind the differential fertility of different ethnic stocks—for example behind the differences in crude birth-rates of negroes and whites in the United States, but it is doubtful if this is the true explanation. As a general rule differences in birth-rates can be explained away by occupational differences and by differences in social customs. Pearl's figures on the effects of contraception on the fertility of whites and negroes show not only a remarkable similarity in the innate natural fertility of the two groups, but also that the same kind of relationships between contraception and mean pregnancy rates exists in comparable economic classes taken from both.†

Pathological Factors

For obvious reasons a genetically-determined low breeding capacity would be difficult to recognize in any given individual. Fortunately, however, most patients under treatment for sterility present some diagnosable pathological or congenital abnormality. As a general rule, several contributory causes, both male and female, determine the sterility of any given marriage. Female factors predisposing to sterility outnumber corresponding male factors in the ratio of two to one,* but there are estimates which attach an even greater share of the blame to the male. Sometimes his incapacity is due to inefficient spermatogenesis, following on, as is now believed, inefficient endocrine functioning of the anterior lobe of the pituitary. Sometimes it is due to some congenital defect which prevents the proper introduction of the sperm. More usually, however, male sterility is due to an inflammatory disease—for example, venereal diseases and mumps—having produced changes in the reproductive tract incompatible with fertility. Corresponding abnormalities lead to sterility in women, in whom congenital abnormalities of the reproductive tract are at least as common as in the male, and in whom inflammatory diseases, new growths, and other disorders of the reproductive tract—all conditions partly or wholly incompatible with fertility—are probably commoner. Thus sterility in women is sometimes due to imperfect gametogenesis, sometimes to difficulties of fertilization, sometimes to an inability to carry through with gestation—a not uncommon disability which frequently passes unnoticed since miscarriages, it is generally believed, occur mostly in the earliest stages of pregnancy.

Dietary Factors

Before passing on to discuss the essential physiology of conception, there is one last point which requires mention—namely the effect of dietary deficiencies on fertility. Experimental work on laboratory animals—in particular, rats—has shown that reproduction is impossible if animals are maintained on inadequate diets.† Two factors which have been found to be indispensable are Vitamin A and Vitamin E. The physical changes which occur in the animal, and in the reproductive organs particularly, following deprivation of these two accessory dietary factors are very constant. Vitamin E has been shown to be a specifically sex

* Hammond, J. 1934. *Harper Adams Utility Poultry Journal, 19.*

† Pearl, R. 1934. *Human Biology, 6,* 355.

* Meaker, S. R. *Loc. cit.* p. 41.

† See Evans, H. M. 1932. *J. Amer. Med. Assoc, 99,* 469.

—— 1932. *Amer. J. Physiol., 99,* 477.

vitamin, the main and almost only effects of its absence being resorption of fœtuses and degeneration of testicular epithelium. The specific change in the reproductive organs following deprivation of Vitamin A is also testicular degeneration. Vitamin E occurs in such foods as fresh lettuces and cereals and is probably never missing from any human diet.

Man is notoriously capable of reproduction even in states of considerable inanition, for example that which accompanies either advanced cancer or tuberculosis. Nevertheless Meaker, a leading expert in the treatment of sterility, believes that many instances of human infertility can be cured by making corrections in the diets of the people concerned.

THE PHYSIOLOGY OF FERTILIZATION

Such then are the physiological factors which set general limits to fertility, and the pathological conditions, largely uncontrollable, which tend to reduce human fecundity still further within these limits. We can now examine, against the background I have roughly sketched, the mechanism of fertilization itself. Recent research has shown that the conditions for effective fertilization are much more fixed and specific than is generally supposed; they must be properly understood if the most fundamental limiting factors to fertility are to be appreciated. Effective fertilization demands the meeting of a viable sperm and a viable ovum, and it is therefore necessary to know the time of ovulation in the menstrual cycle, the length of life of the ovum, and the length of life of the sperm, in order to define the conditions necessary for conception.

The Time of Ovulation

Ovulation is a spontaneous event which occurs only once in each menstrual cycle. This fact has been established by experimental work on isolated mature monkeys, and it is not controverted by any sound clinical data. The view is sometimes advanced that although spontaneous regular ovulation may be the rule, the human female sometimes ovulates at irregular times as a result of the stimulus of coitus. A corresponding mechanism of ovulation is the normal characteristic of ferrets and rabbits. To my knowledge, the hypothesis as it refers to human beings has never been supported by any adequate data; on the other hand, as both Hartman and Knaus have argued,* it is incompatible with a large number of fully reliable facts. Two further considerations make it an improbable hypothesis. The first is the established conclusion, to which I have already referred, that women, like Old World monkeys, are far more prone not to ovulate in any given menstrual cycle than to ovulate too readily. The second is that ovulation is an event which can occur only at the end of a phase of follicular maturation. All the acceptable histological data, both from human beings and from subhuman Primates, indicate that follicles normally ripen to the point of bursting only during a brief part of the middle period of the cycle. This fact clearly limits the applicability of the hypothesis we are discussing. Even assuming that coitus could stimulate a ripe follicle to burst, ovulation brought about in this way would occur only during the period when ovulation normally takes place independently of the stimulus of coitus.

This period, as I have just indicated, is as a rule confined to the middle of the cycle. A great deal of evidence supports this conclusion. Some of it is derived from the study of monkeys, and some has been obtained from the study of clinical material and clinical records. As several investigators have in recent years summarized the evidence in detail,† it is unnecessary here to do more than

* Hartman, C. G. 1932. in *Sex and Internal Secretions*. Edited by Edgar Allen. Baltimore. Williams and Wilkins.

Knaus, H., 1934. *Periodic Fertility and Sterility in Women*. Vienna. Maudrich.

† See, for example, Hartman, C. G. 1932. In *Sex and Internal Secretions*.

—— 1933. *Amer. J. Obst. Gynec.*, *26*, 600.

Knaus, H., *Loc. cit.*

Zuckerman, S. 1930. *Proc. Zool. Soc.*, London, p. 691.

Shaw, W. 1934. *Brit. Med. J.*, i, 7.

refer to the variety of observations on which the conclusion rests. Observations on monkeys, which have essentially the same kind of menstrual cycle as women, comprise: (*a*) direct inspection of the ovaries at different times of the cycle, (*b*) histological examination of ovaries removed at known times of the cycle, or recovered from animals which died on known menstrual dates, (*c*) rectal palpation of the ovaries throughout the cycle, (*d*) observation of the external sexual-skin cycle (after preliminary establishment of its direct relation to the ovarian cycle) and (*e*) controlled matings. Observations on women mainly comprise (*a*) investigations of the endometrial changes that are correlated with the ovarian cycle. There are also (*b*) naked-eye observations of ovaries during operations performed at known times of the cycle, (*c*) histological studies of ovaries, (*d*) a few data on the recovery of ova from the uterine tubes, to which I shall refer again later, and (*e*) some indirect but very striking data provided by Knaus on the uterine responses to pituitrin. Knaus first ascertained that after ovulation the rabbit uterus becomes refractory to pituitrin, and by extirpation experiments he was able to show that its failure to respond to this stimulus is due to the presence of a corpus luteum. Uterine contractility thus provides an index of ovulation, and investigation of the motility of the healthy human uterus led to the conclusion that " in women with normal reproductive physiology ovulation always takes place on the fifteenth day before the onset of the period." A corresponding conclusion is also indicated by investigations of the urinary excretion of certain of the sex-hormones.*

There is no need for me to quote other, less precise, observations on human beings which also support the conclusion that ovulation is a spontaneous event occurring about the middle of the menstrual cycle. I am also doubtful of the value of attempting as yet to define the time of ovulation with any great precision. Knaus' definite conclusion has, however, already been quoted. Ogino supports him in defining the time of ovulation with reference to a succeeding menstruation (twelve to sixteen days before),* and both emphasize the view that the interval between ovulation and the onset of the next menstrual period is more or less fixed, however irregular the whole menstrual cycle may be in total length. Consequently it is possible to define even for irregular cycles the period in which ovulation occurs. Some purpose may be served by quoting Knaus in full on this point. " The ovulation date of an irregular cycle is that period of time which falls between the two ovulation days of the shortest and the longest cycles respectively, the cycles being recorded for at least twelve months." Ogino's definition is not widely different, and both Knaus and Ogino declare that it is possible to make predictions as to conception on the basis of their estimates of ovulation. Their claim has been both disputed† and supported,‡ but on the whole it must be admitted that surprisingly little has been done either to refute or substantiate a conclusion which is clearly of the utmost social importance.

The stand taken by both Knaus and Ogino is that women can conceive only during a brief period in the middle of the cycle, the period being limited by the short lives of the ovum and sperm, a question which I shall shortly discuss. Armed with case-histories, both Knaus and Ogino claim that sexual behaviour can be regulated according to their conclusions. The criticisms of their opinion are based on both clinical and scientific grounds. It is not uncommon, for example, to criticize the theory by opposing to it instances in which conception is believed to have resulted from isolated coitus occurring outside the so-called " safe period." Siegel's famous war-time studies§ and Dickinson's much-quoted conclusions¶ are weapons that have been often

* Kurzrok, R., Kirkman, I. J., and Creelman, M. 1934. *Amer. J. Obst. Gynec.*, p. 319.

* Ogino, K. 1930. *Zentralbl. f. Gyn.*, 54, 464. 1932. *Ibid.*, 56, 721.

† See, for example, Fetscher, R. 1933. *Deuts. med. Wschr.*, 59, 812.

‡ See, for example, Latz, L. J. 1935. *J. Amer. Med. Assoc.* 105, 1,241.

§ Siegel, P. W. 1915. *Deuts. med. Wschr.*, 41, 1,251. —— 1916. *Münch. med. Wschr.*, 6, 748.

¶ Dickinson, R. L. 1927. *Amer. J. Obst. Gynec.*, 14, 718.

used for this purpose, and it would perhaps be as well if the views of the last named author were quoted here. " There is general agreement," writes Dickinson, " on five matters: (1) Conception can occur at any part of the month. (2) There is very marked difference between favourable and unfavourable periods. (3) The week or ten days following menstruation is the time of greatest likelihood of conception. (4) The week preceding menstruation presents the least likely chance of conception, averaging about 7 per cent. or in various lists 3, 6, 9, 9, 3, 10 per cent. (5) Conception during menstruation is comparatively frequent, about 13 per cent."

While I do not wish to be as sweeping as Hartman in brushing aside as valueless the testimony of women regarding the times and frequency of coitus, I must confess to the conviction that information obtained after the event, as in the case of Dickinson's study, can hardly be as reliable as that secured from individuals whose attention is focussed on Knaus' and Ogino's views on conception, and whose behaviour is planned one way or the other in relation to them. With this expression of personal opinion I must couple the hope that before long, enough properly collected clinical data will be available to give a definite answer to the question at issue.

There are only two criticisms of the views of Knaus and Ogino which to my knowledge have emanated from laboratory workers. The first, by Evans and Swezy,* attempts by indirect methods to prove that ovulation in Man can occur at any time of the cycle, but it is a criticism that does not survive close examination.† The second is a physiologically important criticism made by Hartman.‡ Both Knaus and Ogino regard the post-ovulation or luteal phase of the menstrual cycle as being far more stable in length than the pre-ovulation or follicular phase, to whose variations they ascribe the major irregularities of the total cycle. Hartman contests this point. His data are derived from rectal palpation of the ovaries of Rhesus monkeys, and show that the luteal phase in this species of Old-World Primate is much more variable in length than the follicular phase. Hartman is of the opinion that his data should be regarded as more reliable, from the point of view of inferring the human condition, than the clinical data gathered by both Ogino and Knaus. There are however other data, derived from the study of baboons, which do not support his view, but fall into line with the conclusions of those who have studied the human cycle.

The female Hamadryas baboon is an animal whose ovarian phases can be followed by observing the cycle of swelling of the skin and subcutaneous tissues of the genital region. At the beginning of menstruation, which marks the beginning of a cycle, this so-called " sexual skin " is inactive. About the second or third day it begins to swell, until a considerable tense protuberance is formed, which shortly after the mid-point of the cycle suddenly collapses, and is quickly resorbed. The sexual skin then remains quiescent until the onset of the next period of menstrual bleeding. It was found that the subsidence of swelling coincides with ovulation,* and thus an easy method was available for determining its occurrence. Using the phases of the sexual skin as a basis for estimation, the mean length of the luteal phase in forty-eight cycles of *Papio hamadryas*, the sacred baboon, proved to be 15·1, P.E. 0·24 days, the σ for the luteal phase distribution being 2·47; the mean of the follicular phase was 17·1, P.E. 0·35, days, the σ for the distribution, 3·49.† I have recently had the opportunity of repeating these observations on four Hamadryas baboons kept under laboratory conditions. The data for twenty-five cycles‡ again show that the luteal phase in this

* Evans, H. M., and Swezy, O. 1931. *Amer. J. Physiol.*, *96*, 628.

† See Zuckerman, S. 1932. *Brit. Med. J.*, ii, 1,093.

‡ Hartman, C. G. 1933. *Amer. J. Obst. Gynec.*, *26*, 600.

* Zuckerman, S. 1930. *Proc. Zool. Soc.*, London, p. 691.

† Zuckerman, S., and Parkes, A. S. 1932. *Ibid.*, p. 139.

‡ A single irregular cycle in which the changes in the sexual skin did not follow a normal course has been left out of the calculations.

species of Primate is less variable than the follicular phase, as Knaus and Ogino believe it to be in the case of Man. The actual figures are: luteal phase mean, 14, P.E. 0·256, days, σ for distribution, 1·9: follicular phase mean, 19·84, P.E. 0·66, days, σ for distribution, 4·9. In the circumstances it seems questionable whether Hartman is justified in the inference he draws.

Survival of the Ovum

If the hypothesis that the human female is fertile only during a fixed and limited part of each cycle is sound, it is perfectly plain that the ovum can have but a very short life. And it is equally obvious that even were the time of ovulation not fixed, which is contrary to the bulk of present evidence, women would still be infertile during the greater part of each cycle if the mammalian ovum were short-lived. The evidence, though not abundant, is entirely in favour of this latter proposition.

It is true that this evidence is derived mainly from observations on animals, but there is one important set of data which was obtained from study of clinical material.* Some clinicians, who were desirous of securing shed human ova for investigation, examined the ovaries and tubes of some ninety gynæcological patients who were operated on at known times of the cycle. Only five definitely recognizable ova were collected, two coming from the same patient. These two ova, and a third, were collected on the fifteenth day of the cycle, the third ovum being in a degenerated condition. The fourth ovum, collected on the fourteenth day, was quite degenerated, as was probably the fifth, collected on the sixteenth day. Three other doubtful ova were also collected, one on the fifteenth and two on the sixteenth day of the cycle, which, if ova, were in an advanced phase of degeneration. When it is remembered that some ninety patients were examined, and only these few ova obtained, it is perfectly plain that we are here provided with strong evidence that ovulation in women usually occurs about the middle of the cycle, and that the shed ovum has an extremely short life, perhaps only of some hours.

This conclusion is amply supported by the only laboratory experiment on the subject which I need quote here.* The rabbit is an animal that ovulates, not spontaneously, but approximately ten hours after coitus. Rabbits were made to ovulate by being mated with vasectomized males, and then by subsequent introduction of sperms, the life of the shed ova was studied. The experiment clearly showed that conception is impossible if insemination occurs more than six hours after the rupture of the follicles. The result of this investigation agrees well with the conclusions of several others on widely different mammals.

It is generally believed that a liberated ovum takes about three days to pass from the ovary, down the tube and into the uterus. Consequently, since the life of the ovum appears to be so short, fertilization, when it occurs, must take place either at the mouth of the tube or in its most distal part. If viable sperms were always present in that region, fertilization would follow every ovulation, and it is therefore necessary to enquire about the speed with which sperms ascend the female reproductive tract, about the number of sperms that are necessary to ensure the fertilization of any single ovum, and about the length of time sperms remain viable.

Physiology of the Sperm

Experimentalists have found no difficulty in answering the question about the speed with which sperms ascend the female reproductive tract, the simple expedient of examining the uterus and tubes of recently mated rats, rabbits, and other mammals, having provided a definite answer.† In rats, sperms reach the ovaries within sixty seconds of mating. In dogs and rabbits their passage through the reproductive tract may not be so rapid, but it is certainly a matter of

* Allen, E., and co-workers. *Loc. cit.*, p. 40.

* Hammond, J. 1925. *Reproduction in the Rabbit.* Edinburgh. Oliver & Boyd.

† See Hartman, C. G. 1932. In *Sex and Internal Secretions.*

minutes, or at most an hour or two. There are no data on this question for either Man or monkeys, and in the absence of contrary knowledge, one must assume that the transport of sperms takes relatively as short a time in them—provided that the process of insemination follows a perfectly normal course.

The second question, the number of sperms required to ensure the fertilization of a single ovum, has received a fairly exact answer both from clinical and from experimental work. A single normal ejaculate in Man varies between 3 and 6 c.c.s, and each cubic centimetre contains between 75,000,000 and 200,000,000 spermatozoa. These incredibly high figures achieve some significance when one learns that the Meaker Clinic for Sterility, the most famed clinic for the treatment of sterility in the world, knows of no instance of human pregnancy occurring where the sperm count was below 60,000,000.* This finding receives corroboration from experiments on the fertilizing powers of different dilutions of semen on female rabbits previously mated with vasectomized males.† Full concentrations of semen give full fertility, lower concentrations give smaller litters, until a dilution is reached, in which the number of sperms is still high (100,000 per 3 c.c.s), which is completely ineffective from the point of view of conception.

Although it takes but a single sperm to fertilize a single ovum, it is not difficult to understand why so many sperms have to be ejaculated in order to secure fertilization. In their passage from the vagina to the upper part of the uterine tubes, the sperms may become lost in innumerable glandular crypts and folds of mucous membrane. It is even likely that many sperms are lost in the peritoneal cavity. Consideration of the amazing disproportion in the ratio of liberated human sperms to liberated ova leads to an interesting conclusion, which, unfortunately, has to be highly speculative for want of data.

It would seem, if Man is regarded as the highest product of organic evolution, that there has been an increasing waste of male germ cells as the evolutionary pattern has unfolded itself. The ratio of sperms to ova among fish in general cannot be nearly as disproportionate as it is in Man. In many viviparous species, for example, *Xiphophorus helleni Regan*, mature females, previously mated and then isolated, may give birth to as many as seven litters of up to 100 young each over a period of a year, fertilization in each case having been effected by sperms stored from the previous insemination.* Furthermore, insemination in many fish occurs during a definite breeding season, when the chances of fertilization are high. The young of frogs, again, are so numerous that it is difficult to imagine so enormous a disparity in the relation of male and female gametocytes as occurs in Man; moreover fertilization is to some extent ensured, as it is in the case of fish, by the occurrence of breeding seasons. The same is true of reptiles, even though the number of young they produce is not as great. Birds, too, show the same general characteristics; in some, successive ova may be fertilized over a relatively long period by sperms deposited at a previous insemination. In the domestic hen this period is as long as twenty days, and in the domestic turkey a single insemination serves for a whole laying season.† Compared with most, if not all, his fellow mammals, Man again shows himself outstanding in regard to the waste of gametocytes. Most mammals can give birth to large litters after a single insemination, and even those that produce only a single young, like those that are more fruitful, differ from Man in usually breeding only during restricted mating seasons, and at oestrous periods when sperms are certain to meet viable ova. And finally one sees that Man even differs from the majority of his fellow Old World Primates, which although they mate and may breed at all times of the year, nevertheless are so controlled physiologically (for example, by means of a sexual skin)

* Meaker, S. R. *Loc. cit.*, p. 41.
† Walton, A. 1927. *Proc. Roy. Soc.*, B., *101*, 303.

* Van Oordt, G. J. 1928. *Tijdschr. Ned. Dierk. Ver., Helder*, 3rd Ser., *1*, 1.
† Crew, F. A. E., 1926. *Proc. Roy. Soc.*, Edin., *46*, 230.

that mating during each menstrual cycle is most frequent when the chances of conception are highest.* It is difficult to avoid regarding breeding seasons and periods of oestrus teleologically as adaptations which limit the waste of gametocytes in the animal kingdom. Nor is it difficult to realize that compared with most other living things, the behaviour of the human species is peculiarly badly directed physiologically with regard to optimum times of conception. In the circumstances frequency of coitus can be regarded as a necessary means of achieving fertilization. Although their sexual behaviour is still to some extent under oestrous control, even subhuman Primates mate at all times of the menstrual cycle.†

Conception often, in the writings of novelists, results from an isolated sexual act, but in real life this is probably exceptional. Meaker, to whose clinical experience I have already had occasion to refer, has written very clearly on this point. "Undoubtedly there are human matings in which a single act of coitus, or at most coitus repeated at intervals throughout one menstrual month, would infallibly produce conception, but they are exceptions. Most couples who succeed in reproducing do so in spite of certain imperfections in the conceptive mechanism . . . most people are relatively and not absolutely fertile."‡ It is not surprising that many writers believe that a general decreased incidence of coitus may be partly responsible for declining birth-rates.

Survival of the Sperm

My emphasis of the necessity for insemination to occur close to or at the time of ovulation is based on the view that the human sperm, like the ovum, is very short-lived. The period of viability of the sperm is clearly of the greatest importance. If sperms could live in the female reproductive tract for three weeks, as some earlier writers claimed, there would be just reason for regarding women as dangerously fertile. Those sperms which had reached the distal end of the tubes would be always ready to fertilize any shed ova, while those that had not, would presumably continue wandering round the female tract until they had. But all the acceptable data about mammalian sperms is completely against this view, and while it is perhaps impossible to define the period that the human sperm can live in the female body with any accuracy, it is safe to say that it cannot be longer than two or three days at the most.

I do not propose to discuss more than part of the evidence on which this conclusion rests.* Before, however, considering this evidence, it is interesting to note that there are animal species in which sperms are undoubtedly long-lived. Bees are well-known examples. Some viviparous fishes and certain birds, to which I have already referred, are others. The only two mammals whose sperms, some claim, live for a long period in the body of the female are bats and badgers. Both these animals are said to mate in the autumn, and it is stated that the sperms remain dormant in the reproductive tract of the female until the succeeding spring, when ovulation occurs. This view of the process of fertilization in these two species is, however, not established.

Modern views on the viability of mammalian sperms in general, and of human sperms in particular, derive both from observations on the behaviour of sperms recovered from the female genital tract after coitus, and from observations on the behaviour of sperms collected directly from

* Zuckerman, S. 1930. *Loc. cit.*, p. 45.
Zuckerman, S. 1932. *The Social Life of Monkeys and Apes.* London. Kegan Paul.
Ball, J., and Hartman, C. G. 1935. *Amer. J. Obst. Gynec.*, *29*, 117.

† The opinion has been expressed by Yerkes, R. M., and Yerkes, A. W. (in *A Handbook of Social Psychology*, edited by Carl Murchison, 1935, Worcester, Mass., Clark Univ. Press) that sexual behaviour among chimpanzees is less engrossing and frequent than I found it to be among baboons. Their opinion hardly applies to some observations that have been recorded in the literature. For example, Schultz, A. H., and Snyder, F. F., in a recent publication (*Bull. Johns Hopkins Hosp.*, 1935, *4*, 193) tell of a pair of these apes, under investigation in their laboratory, that copulated "fairly regularly three and more times daily for approximately six months"—and for several weeks after the beginning of pregnancy.

‡ Meaker, S. R. *Loc. cit.*, p. 41.

* For further information see Knaus, H. *Loc. cit.*, p. 43. Hartman, C. G. In *Sex and Internal Secretions.*

the male and kept *in vitro*. Hammond and Asdell found that sperms cannot live in the genital tract of rabbits longer than thirty-two hours.* Huehner's studies† show that human sperms, like those of Rhesus monkeys,‡ do not as a rule live more than two hours in the unfavourable secretions of the vagina, and, moreover, only a few feebly motile sperms could be collected from the uterus seven days after coitus. The motility of a sperm does not, however, imply a power to fertilize. Conclusive studies on guinea-pigs, on rabbits and on men, have proved that sperms may be fully motile and yet completely infertile.§ Human sperms have remained motile for six days at room temperature when kept in their natural medium, and as many as twenty-one days when kept at room temperature in buffered solutions.¶ Numerous experiments, which are ably summarized by Knaus,‖ have, however, shown that at body temperature sperms rapidly lose their fertility, and the general conclusion is that the sperms of all mammals whose testes are enclosed in an external scrotum become infertile within forty-eight hours after they are exposed to the normal temperature of the female reproductive tract.

The Need for Work on Primates

I can briefly summarize the statements I have made about the time of ovulation, about the period of survival of the ovum, and about the period of survival of the sperm, by saying that the available information we have about all three problems satisfies the conditions demanded by the hypothesis that women are fertile only during a fixed and brief part of each menstrual cycle. It is necessary, however, to emphasize the fact that much of the experimental data we have on the physiology of the sperm and of the ovum is derived from studies of non-primate mammals. Indeed, apart from reports on the motility of sperms recovered from the human female reproductive tract, the success which Ogino and Knaus claim for the practical application of their view on the "safe period" is the only evidence we have that the periods of viability of the human sperm and ovum are approximately the same as those of the laboratory mammals that have been studied.

Few can be so optimistic as to expect that human beings will regulate their sexual and reproductive lives on the basis of an hypothesis which, however convincing its foundations may be to some, is nevertheless a matter that is still disputed. It is obvious that irrefutable data about human beings will accumulate only when some reliable and easy method is devised for determining the time of ovulation in the human female, and it is to be hoped that the electrometer recently devised by Burr and Lane* will, as they suggest, provide the necessary means for doing this. Until this has been done it is clearly desirable that the survival of the sperm and ovum should be studied, *in vivo*, in some other Old World Primates. Such a study has already been begun, with Hamadryas baboons as subjects.† This animal, as I have already stated, provides in the fluctuations of its sexual skin, an index of the ovarian phases, and by mating females at varying times before and after the subsidence of swelling, an event which is correlated with ovulation, information should be obtained both about the viability of the gametocytes, and about the existence or non-existence of restricted periods of fertility. The few results so far obtained suggest that the Hamadryas baboon does not readily conceive from a single insemination, even when this is made within as few as twenty-four hours either before or after the estimated time of ovulation.

* Hammond, J., and Asdell, S. A. 1926. *Brit. J. Exper. Biol.*, *4*, 155.

† Huehner, M. 1913. *Sterility in the Male and Female, and Its Treatment.* New York. Rebman.

‡ Hartman, C. G., in *Sex and Internal Secretions.*

§ See Hartman, C. G. *Ibid.*

¶ Meaker, S. R. *Loc. cit.*, p. 41.

‖ Knaus, H. *Loc. cit.*, p. 43.

* Burr, H. S., and Lane, C. T. 1935. *Yale J. Biol. & Med.*, *8*, 31.

† I am greatly indebted to the Council of the *Eugenics Society* for the opportunity of pursuing this investigation, and to Professor W. E. Le Gros Clark, F.R.S. for his kindness and generosity in allowing the study to be made in the Department of Human Anatomy, Oxford.

Conclusion

In concluding this lecture it is almost unnecessary to say that a sound knowledge of the conditions of human conception would be of value in planning sexual behaviour, not only from the point of view of limiting births, but also from the point of view of their encouragement. Were such issues as we have been discussing thoroughly established, the times of both normal and artificial insemination could be far better controlled than they can be at present, and it is not unlikely that the incidence of sterility, a problem with which gynæcologists in their practice frequently wrestle in vain, would be materially reduced. There is one last remark that I should like to make. The facts that I have brought before you about the specificity of the conditions that determine conception, may have combined with the knowledge we all have about the dangerously slow rate of human replacement, to make a depressing picture of a hopelessly inefficient human reproductive machine. If they have, I think we can reassure ourselves. It need not be feared that the human potentialities for reproduction are decreasing, for although the conditions for conception may be very specific, there is no evidence that they have become disorganized in the majority of people, or that any diminution has occurred in the inherent fertility of Mankind. Even if present reproduction and replacement rates presage the extinction of the human species, we can therefore expect that when the factors responsible for their trends are thoroughly understood and brought within the realm of control, the human reproductive machine will be fully capable of supplying the living material of a progressive and assured civilization.